# REMARKS

## FORMAL MATTERS:

Claims 1, 3-10, and 15-16 are pending after entry of the amendments set forth herein.

Claims 11-14 have been canceled as being directed to withdrawn subject matter.

Claims 1, 3-7, 9-10 and 16 have been amended. Support for this amendment can be found in the claims as originally filed and throughout the specification at, for example, Figure 1 and Summary.

In particular, Claim 1 is amended to clarify that the method employs a nucleic acid tag that directs and encodes the synthesis of a compound to which it is covalently attached (e.g., see specification page 4, lines 15-18). Claim 1 also is amended to clarify that forming groups of subsets involves providing a pool of nucleic acid tags and then splitting the pool into physically separate subsets or sub-pools on the basis of the specific hybridization sequence in the variable region of each tag. (e.g., see Figure 1, and specification page 4, lines 15-18; page 6, line 29 – page 7, line 5; page 14 line 6 – page 15, line 22, such as page 15, lines 7-8). Claim 1 is further amended to specify that the nucleic acid tag comprises a single stranded DNA sequence, for hybridization purposes (e.g., see Figure 1, and specification page 4, lines 15-18; page 13, lines 15-21). Claim 1 is further amended to specify that the chemical reaction site is covalently attached to the 5' terminus of the single stranded DNA sequence (e.g., see Figure 1 and Figure 2, and specification page 13, line 25 – page 14, line 4; page 16, lines 1-2). Claim 1 is additionally amended to clarify that the hybridization sequences correspond to variable regions, and that each variable region is different for each subset of nucleic acid tags (e.g., see Figure 1, and specification page 6, line 28 – page 7, line 5; page 12, lines 28-33; page 13 lines 1 – 24; page 15, lines 7-8). Claim 1 is also amended to specify that a selected one of a plurality of reagents couples a different chemical subunit or chemical substituent to the chemical reaction site (step (c)) or the reagent-specific compound (step (f)) of each subset of tags under conditions effective to form and produce the next subset (e.g., see, specification pages 15-16, and original claims 3 and 4). Claim 1 is also amended to specify that the reacting involves coupling of a chemical subunit to form a different sequence oligomer or different sequence small-molecule compound (step (f)) (e.g., see, specification page 7, lines 19-24; and page 9,, lines 4-9).

Claims 3 and 4 are amended for antecedence. Claim 4 is also amended to recite small molecules (e.g., see original claim 4, Figure 2, and specification page 5, line 11; page 7 lines 17-24; page 9, lines 4-9; page 18, lines 6-11).

Claim 5 is amended for antecedence and to clarify that the method for making compounds requiring more than 2 synthetic steps involve one or more rounds of pooling, splitting and synthesis as recited in parent Claim 1 (see, e.g., Figure 1, and specification page 6 line 32 – page 7 line 5; page 10, line 31- 11 line 17; page 12 lines 15-19; page 14, lines 7-9; and page 16, lines 24-25).

Claims 6 and 16 is amended for antecedence.

Claim 7 is amended for antecedence and to specify that the adjacent spacer is a constant "C" region (e.g., See Figure 1, and specification page 12, lines 28-33; page 13 lines 1 – 24).

Claim 9 is amended to clarify that "using" in claim 8 refers to using the subpopulation. Support for this amendment is found, for example, in the original claims.

New Claims 17-30 have been added. Support for this amendment can be found in the claims as originally filed and through out the specification, for example, as noted above for, and at Figures 1 and 2, in the Summary.

No new matter has been added and the Examiner is respectfully requested to enter the amendments.

**EXAMINER INTERVIEW**

Applicants wish to express their gratitude to Examiner Liu, Examiner Shultz and Examiner Eberstein for the helpful in-person interview on November 15, 2007 with Dr. James A. Bradburne, and by telephone with the inventor, Professor Pehr B. Harbury. All outstanding rejections of the claims were discussed during the interview, and particularly the rejection of the claims under §112 ¶1, and §112 ¶2, and the prior art rejections. The present amendments and arguments presented herein reflect those presented during the interview, which amendments and arguments the Examiners indicated may be deemed persuasive to place the application in form for allowance.

**WITHDRAWN REJECTIONS**

Applicants express gratitude in the Examiner's indication that previous rejections not reiterated in the present Office Action have been withdrawn.

**REJECTIONS UNDER §112, ¶1**

***Rejections under 35 U.S.C. §112, first paragraph (written description)***

Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. The rejection is avoided in part and traversed in part for the following reasons.

The Office Action asserts that the method claims require genuses of 'nucleic acid tags, chemical reaction sites, reactions or synthetic steps, and reagents' but that neither the specification nor the claims have demonstrated a common structure and/or function for the claimed genuses, and that no representative number of species is demonstrated for the genuses.

First, Applicant notes that the claims in question are method claims, not composition claims, and that the specification need not teach or disclose that which is well known in the art, particularly where the invention claimed is a novel procedure that employs known chemical reactions and a known class or classes of compounds.

Applicant submits that nucleic acids for selective hybridization, nucleic acids with different chemical reaction sites, and reaction conditions and reagents suitable for carrying out the claimed method were well known, and that one of ordinary skill, in possession of Applicant's disclosure would have been apprised as to the nature of the claimed method, and how it is to be carried out. That the specification discloses novel constructs of nucleic acid tags in exemplifying the claimed method (e.g., Figure 1) does not detract from this basic fact. Nor does the fact that the specification exemplifies the use of such constructs in the synthesis of peptides with compatible reagents and conditions, namely Fmoc chemistry (See, e.g., Figure 2, and specification page 16, paragraph 1). Thus Applicant submits that the specification and claims are in synchrony, apprising one of skill in the art as to the nature of the claimed method, and how it is to be carried out.

Second, in the interest of advancing prosecution without conceding to the correctness of the rejection, Applicant has amended the claims (e.g., Claim 1) to limit the nucleic acid tags to DNA, the chemical reaction site to the 5' terminus, and the reagents to those that couple a

"chemical subunit" to the chemical reaction site under conditions effective to form the reagent-specific compound intermediate (step (a) for first synthetic reaction) or to the reagent-specific intermediate (step (f)) so as to form "a different sequence oligomer or different sequence small-molecule compound" to produce the desired subset of nucleic acid tags (e.g., see Specification page 7, lines 19-24; and page 9,, lines 4-9). Thus, without conceding to the correctness of the rejection or forfeiting Applicant's right to pursue claims to the other embodiments disclosed in the specification, Applicant submits that the range of nucleic acid tags, reagents, reactions and conditions for synthesis in accordance with the methods of the invention are well within a scope commensurate with the specification as originally filed, and clearly apprise one of skill in the art as to the nature of the claimed method, and how it is to be carried out.

Third, the Office Action mischaracterizes Applicant's disclosure as "demonstrating no common structure and/or function for the claimed genuses, and that no representative number of species is demonstrated for the genus." Applicant's response to this part of the Office Action is provided below following reiteration of each specific argument put forth in the Office Action.

***Nucleic acid tags***

The Office Action at pages 6-7, bridging paragraph asserts:

> The instant specification is general and prophetic in nature, and does not provide any specific examples of the claimed genus of nucleic acid molecules, chemical reactions, and chemical reagents that are capable of being used with the claimed method. In particular, the specification does not demonstrate what specific nucleic acid sequences are capable of forming the "nucleic acid tags" that would hybridize for the selection steps, and also allowing the chemical reactions to proceed.

Regarding sequences that would hybridize for the selection step, in the interest of expediting prosecution and without conceding to the correctness of the rejection, Claim 1 and the relevant dependent claims are amended to specify that the hybridization sequences are "variable" hybridization sequences capable of "specific hybridization" to a corresponding immobilized sequence. For example, the specification clearly describes that a "variable" hybridization sequence refers to the hybridization sequences which are different for each group of subsets of nucleic acid sequences (e.g., specification page 12, lines 31-32), and "specific hybridization" refers to temperature, ionic strength and/or solvent conditions effective to produce sequence-

specific pairing between a single-stranded oligonucleotide and its complementary-sequence nucleic acid strand, for a given length oligonucleotide (e.g., specification page 7, lines 25-28).

As to sequences that would hybridize for the reaction steps, in the interest of expediting prosecution and without conceding to the correctness of this aspect of the rejection, Claims 1 and 5 have been amended to clarify that the selected hybridization complexes are physically separated from each other and that the immobilized sequence is removed prior to the reaction step.

It also is submitted that in possession of Applicant's specification, one of ordinary skill in the art would have clearly recognized that, as described, a broad range of reagents and conditions could be exploited in Applicant's method for coupling to nucleic acids without impacting hybridization. This includes the attachment of very large molecules, such as antibodies and enzymes to nucleic acids, which was well known at the time the instant application was filed (See, e.g., Corey et al., Bioorganic Chemistry Frontiers 2:1-31 (1999); Pei et al., PNAS (1990), 87(24):9858-62; Corey et al., J. Amer Chem Soc (1989) 111(22):8523-5; Corey et al., Biochemistry (1989) 28(21):8277-86; Corey et al., J Biol Chem (1989) 264(7):3666-9; Zuckermann et al., J Amer Chem Soc (1988) 110(5):1614-15; and Corey et al., Science (1987) 238(4832):1401-3)). In addition, the literature was replete with examples of oligomers and small molecules attached to nucleic acids of all types that are exploited for the nucleic acid's ability to hybridize to its complementary strand (See, e.g., Famuloket al. Top. Curr. Chem. (1999) 202:101-131; Carola et al., Curr. Opin. Chem. Biol. (1999) 3:274-283; Gat et al., In *Templated Organic Synthesis* (Eds.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim 1999, pp. 133-157; Kozlov et al., J. Am. Chem. Soc. (1999) 121:5856-5859; Gat et al., Biopolymers 1998, 48:19; Luther et al, Nature (1998) 396:245-248; Liu et al., Nucleic Acids Res. 1998, 26, 3300; Schmidt et al., Nucleic Acids Res. (1997) 25:4792; Li et al., *Organic reactions in aqueous media*, Wiley, New York, 1997;. Scott, AI.,Tetrahedron Lett. (1997) 38:4961; Bruick et al., Chem. Biol. (1996) 3:49-56; Bruick et al., Chem. Biol. (1996) 3:49; Herrlein et al., J. Am. Chem. Soc. (1995) 117, 10151; Orgel, E, Acc. Chem. Res. (1995) 28:109-118) Herrlein et al., J. Am. Chem. Soc. (1995) 117:10151-10152; and Li et al., Nature (1994) 369:218). For some recent reviews, see Summerer et al., Angew. Chem. Int. Ed. (2002) 41(1):89-90; and Gartner et al., Angew. Chem. Int. Ed. (2002) 41(10): 1796-1800).

The fact that the hybridization sequences of the nucleic acid tags comprise sequences that are different for each group of subsets of nucleic acid sequences and required to selectively hybridize to the corresponding immobilized sequence (common structure and function) is sufficient for comprehending the method as described and claimed, as multiple sequences suitable for this purpose were known or could have been be routinely constructed (See. e.g., Abelson, J. N., Methods in Enzymology 267: 1-483 (1996), and Fitzwater and Polisky, Methods Enzymol 267:275-301 (1996); see also, above-cited references).

In addition, the specification describes by way of example a novel nucleic acid tag that consists of 21 regions of twenty base pairs that contains both constant regions and variable hybridization regions (as further exemplified in Figure 1), that the tags are degenerate relative to each other by virtue of the different variable regions with orthogonal hybridization properties (which is exploitable for selective hybridization purposes at any given step of the method), and are assembled from their constituent building blocks by the primerless PCR assembly method (See, e.g., Specification page 13, lines 22-23).

The Office Action at pages 6-7, bridging paragraph asserts:

> In addition, the instant claims recite "nucleic acid tags" without specifying if the nucleic acid molecules are single stranded or double stranded. In certain method steps (e.g. Claim 10), the steps require nucleic acids to be in the double stranded form for the claimed "restriction" digestion to proceed, because "restriction enzymes" recognizes double stranded nucleic acid molecules. However, throughout the instant claims (e.g. Claim 1), the "nucleic acid tags" seem to be in single stranded forms, because the "nucleic acid tags" are hybridized to the "immobilized nucleotide sequence". Thus, for "nucleic acid tags" in the single stranded form, the instant specification has not shown possession of the method of "restriction digestion". For double stranded "nucleic acid tags", the instant specification has not shown possession of how the hybridization steps can occur.

In response, one of ordinary skill in the art would have been well aware of the conditions for nucleic acid hybridization, and that hybridization of the nucleic acid tag to the immobilized complementary sequence can be carried out starting with either single or double stranded material – its simply a matter of using well known and routine hybridization conditions suitable for such purpose (See, e.g., Southern, EM et al., Nucl. Acids Res. 22(8) 1368-1373 (1994)).

Whether certain steps employ hybridization and others restriction digestion does not detract from apprising one of skill in the art as to the nature of the claimed method, and how it is to be carried out (e.g., if the material is single stranded, one of ordinary skill would have recognized that it can easily be made double stranded by any one of a number of known techniques and vise versa)(See, e.g., Southern, EM et al., Nucl. Acids Res. 22(8) 1368-1373 (1994)). This was common knowledge.

In the interest of expediting prosecution and without conceding to the correctness of this aspect of the rejection, Claims 1 and 5 have been amended to specify that the immobilized sequence is removed after splitting, and Claim 10 has been amended to recite a PCR amplification step.

***Chemical reactions***

The Office Action at page 7 asserts the following:

> It is known in the art that certain chemical reactions would destroy the integrity of nucleic acid molecules. For example, Greene et al (Protective Groups in Organic Synthesis. 3rd ed. NY. 4/1999; p.v, pp. 1-5, p. 502-503 only) teaches "when a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked" (p. 1, lines 1+). Greene et al also teach the protection of the nitrogen bases including adenine, cytosine, etc. are needed (p. 502, last para). Thus, in chemical synthesis such as generation of oligonucleotides (i.e. addition of nucleotides to a nucleic acid strand), protection groups of the "multifunctional compounds" (such as nucleic acids) are needed to protect the integrity of the generated nucleic acids. The instant specification does not provide any guidance to the reaction condition under which the "first" and "second" or any subsequent "synthesis steps" are carried out. It is not shown how the integrity of the nucleic acids would be preserved for conducting subsequent or concurrent hybridization reactions. Furthermore, even with the appropriate protection groups such as carbamates formed on the nucleotide bases, problems such as interference with proper base pairing during hybridization reaction would still exist.

In the interest of expediting prosecution and without conceding to the correctness of this aspect of the rejection, Claim 1 has been amended to specify that the nucleic acid tag is DNA, and to clarify that the reaction steps are carried out under conditions effective to produce the

desired product (e.g., see original claims 3 and 4, and specification page 15, line 34 – page 16, line 18); Claims 1 and 5 also have been amended to specify that the immobilized sequence is removed after splitting, prior to the reaction step. Thus the concern over using chemical reaction conditions that may be incompatible with the hybridization conditions is eliminated.

Regarding Green et al., it is submitted that in possession of Applicant's specification, one of ordinary skill would not set out to defeat the purpose of the claimed method, for example, by choosing chemical reactions or conditions known to destroy the integrity of nucleic acid tag (e.g., strong acidic conditions, such as those used to remove some protecting groups from amino acids cited in Green et al, *supra*).

Applicant further submits that the specification clearly would have apprised one of ordinary skill in the art as to the nature of the claimed method, and how it is to be carried out at the time the application was filed, given the fact that the method, as described, was perfectly suited for employing multiple different types of known chemical reactions using known classes of compounds. For example, it was well known that a broad range of reagents and conditions were available and suitable for carrying reactions and syntheses on, and compatible with unprotected nucleic acids (See, e.g., Chu, BC, et al. Nucleic Acids Research 11(18):6513-6529 (1983); "Oligonucleotide Synthesis: A Practical Approach", ed. M. J. Gait, JRL Press, New York, N.Y. (1990); and Green et al. *supra* and Green et al., "Protective Groups in Organic Synthesis. 2nd ed. NY 1991). See also, Famuloket al. Top. Curr. Chem. (1999) 202:101-131; Carola et al., Curr. Opin. Chem. Biol. (1999) 3:274-283; Gat et al., In *Templated Organic Synthesis* (Eds.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim 1999, pp. 133-157; Kozlov et al., J. Am. Chem. Soc. (1999) 121:5856-5859; Gat et al., Biopolymers 1998, 48:19; Luther et al, Nature (1998) 396:245-248; Liu et al., Nucleic Acids Res. 1998, 26, 3300; Schmidt et al., Nucleic Acids Res. (1997) 25:4792; Li et al., *Organic reactions in aqueous media*, Wiley, New York, 1997;. Scott, AI.,Tetrahedron Lett. (1997) 38:4961; Bruick et al., Chem. Biol. (1996) 3:49-56; Bruick et al., Chem. Biol. (1996) 3:49; Herrlein et al., J. Am. Chem. Soc. (1995) 117, 10151; Orgel, E, Acc. Chem. Res. (1995) 28:109-118) Herrlein et al., J. Am. Chem. Soc. (1995) 117:10151-10152; and Li et al., Nature (1994) 369:218). For some recent reviews, see Summerer et al., Angew. Chem. Int. Ed. (2002) 41(1):89-90; and Gartner et al., Angew. Chem. Int. Ed. (2002) 41(10): 1796-1800).

Lastly, the specification describes by way of example a method for carrying out synthesis reactions on the nucleic acid tags using compatible reagents and conditions, namely Fmoc chemistry, thus apprising one of skill in the art as to the nature of the claimed method, and how it is to be carried out (See, e.g., specification page 16, paragraph 1).

***Chemical reaction site***

The Office Action at page 6 asserts the following:

> The instant specification defines the term "chemical reaction site" as "a chemical component capable of forming a variety of chemical bonds including, but not limited to ..." (p. 9, para 3), which essentially encompasses any chemical entity that can form bonds.

In response, Applicant notes that the section of the specification referred to by the Office in this aspect of the rejection provides a specific list that defines the chemical reaction site. This list is exemplary and includes chemical reaction sites that are capable of forming the following bonds: amide, ester, urea, urethane, carboncarbonyl bonds, carbon-nitrogen bonds, carbon-carbon single bonds, olefin bonds, thioether bonds, and disulfide bonds (See specification page 9, paragraph 3). Applicant submits that one of ordinary skill would have clearly understood the chemical reaction sites as described.

Indeed, multiple reagents and methods were well known for the generation of chemical reaction sites on nucleic acids at the 5' or 3' terminus and/or internally for forming multiple types of bonds to a broad range of other compounds (See, e.g., Glen Research Catalog #l0-1926-xx, 1991; Glen Research, *User's Guide to DNA Modification and Labeling*, 1999; Chu, BC, et al. Nucleic Acids Research 11(18):6513-6529 (1983); "Oligonucleotide Synthesis: A Practical Approach", ed. M. J. Gait, JRL Press, New York, N.Y. (1990); Famuloket al. Top. Curr. Chem. (1999) 202:101-131; Carola et al., Curr. Opin. Chem. Biol. (1999) 3:274-283; Gat et al., In *Templated Organic Synthesis* (Eds.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim 1999, pp. 133-157; Kozlov et al., J. Am. Chem. Soc. (1999) 121:5856-5859; Gat et al., Biopolymers 1998, 48:19; Luther et al, Nature (1998) 396:245-248; Liu et al., Nucleic Acids Res. 1998, 26, 3300; Schmidt et al., Nucleic Acids Res. (1997) 25:4792; Li et al., *Organic reactions in aqueous media*, Wiley, New York, 1997;. Scott, AI.,Tetrahedron Lett. (1997) 38:4961; Bruick et al., Chem. Biol. (1996) 3:49-56; Bruick et al., Chem. Biol. (1996) 3:49; Herrlein et al., J. Am. Chem. Soc. (1995) 117, 10151; Orgel, E, Acc. Chem. Res. (1995) 28:109-118) Herrlein et al., J. Am.

Chem. Soc. (1995) 117:10151-10152; and Li et al., Nature (1994) 369:218). For some recent reviews, see Summerer et al., Angew. Chem. Int. Ed. (2002) 41(1):89-90; and Gartner et al., Angew. Chem. Int. Ed. (2002) 41(10): 1796-1800).

The Office Action at page 7 asserts the following:

> The instant claims also encompass attaching the "chemical reaction site" anywhere on the "nucleic acid tags". For example, a reaction moiety (such as a small organic molecule) can be attached at the middle of the hybridization sequences. It may be likely that the reaction moiety would interfere with the hybridization reaction (e.g. attachment onto the nucleotide base), or the formed hybridization complex may interfere with the chemical reaction.

As noted above, multiple types of nucleic acids modified with a chemical reaction site at the 5' or 3' terminus, or internally (for coupling a compound to the nucleic acid through the chemical reaction) were well known, and exploited for hybridization. However, in the interest of expediting prosecution and without conceding to the correctness of this aspect of the rejection, Claim 1 has been amended to specify that the chemical reaction site is at the 5' terminus.

In view of the amendments to the claims and the remarks made herein, this rejection of Claims 1, 3-10, 15 and 16 under 35 U.S.C. §112, first paragraph for written description may be withdrawn.

***Rejections under 35 U.S.C. §112, first paragraph (enablement)***

Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. §112, first paragraph. The rejection is avoided in part and traversed in part for the following reasons.

The purpose of the enablement provision is to assure that the inventor provides sufficient information about the claimed invention to allow a person of skill in the field of the invention to make and use it without undue experimentation, relying on the patent specification and the knowledge in the art. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 1001 1006 (Fed. Cir. 1991 ). A single illustrative embodiment may suffice when the invention claimed is a novel procedure for carrying out a known chemical reaction, or for using a known class of compounds. *In re Herschler*, 591 F.2d 693, 700-01, 200 USPQ 711, 717 (CCPA 1979); *In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 323, 326-27 (CCPA 1981); *In re Kaslow*, 707 F.2d 1366, 707 F.2d 1366, 217 USPQ 1089 (Fed. Cir. 1983).

As the Examiner noted, M.P.E.P. §2164.01, outlines the factors to be considered in a determination of undue experimentation, including (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. See also In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988). As also stated in M.P.E.P. 521 64.01, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I. T. v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1987).

The Office Action asserts that, because the specification, while being enabling for using certain nucleic acids as tags for selecting certain reaction products (attached to the nucleic acid tags), does not reasonably provide enablement for using any other nucleic acid molecules to generate any chemical entities attached thereon.

In the interest of advancing prosecution without conceding to the correctness of the rejection, Applicant has amended the claims (e.g., Claim 1) to limit the nucleic acid tags to DNA, the chemical reaction site to the 5' terminus, and the reagents to those that couple a "chemical subunit" to the chemical reaction site under conditions effective to form the reagent-specific compound intermediate (step (a) for first synthetic reaction), or to the reagent-specific intermediate formed in the first reaction (step (f)), so as to form "a different sequence oligomer or different sequence small-molecule compound" to produce the desired subset of nucleic acid tags (e.g., see Specification page 7, lines 19-24; and page 9, lines 4-9).

Turning to the specific rejections, Applicant submits that nucleic acids for selective hybridization, nucleic acids with different chemical reaction sites, and reaction conditions and reagents suitable for generating a broad range of different sequence oligomer or different sequence small-molecule compounds attached thereon were well known at the time the application was filed, and that one of ordinary skill, in possession of Applicant's disclosure would have been able to make and use the methods of the invention as currently claimed without undue experimentation.

The specific rejections are reiterated below, followed by Applicant's response.

The Office Action at pages 9-10 asserts the following with regard to the breadth of the claims:

> The breadth of the claims seems to encompass various steps and reagents. Claim 1 recites a genus of methods requiring a genus of "nucleic acid tags", a genus of "chemical reaction sites", a genus of "reactions" or "synthetic steps", and a genus of "reagents". Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genuses of "reagents" (or compounds), "nucleic acids", "reactions". Thus, the claims are drawn to any nucleic acid molecules, any chemical reaction sites (or any compounds), any chemical reactions, etc. In addition, no representative numbers of species for each claimed genus is provided to show possession of the claimed genuses.

First, the claims in question are method claims, not composition claims, and the specification need not teach or disclose that which is well known in the art, particularly where the invention claimed is a novel procedure that employs known chemical reactions and a known class or classes of compounds. Id. *In re Herschler.*

Second, the claims have been amended to limit the nucleic acid tags to DNA, the chemical reaction site to the 5' terminus, and the reagents to those that couple a chemical subunit to the tags under conditions effective to form a "different sequence oligomer or different sequence small-molecule compound" attached to a nucleic acid tag. As described in the specification, "different sequence oligomer" are oligomers, and "different sequence small-molecule compounds" are small organic molecules, both of which are representative of typical molecules found in small molecule libraries (See, specification page 7, lines 19-24, and page 9, lines 4-9).

Lastly, the specification discloses nucleic acid tags that exemplify those suitable for carrying out the claimed method (e.g., Figure 1), as well as use of the tag-directed synthesis of peptides with compatible reagents and conditions illustrated by well known Fmoc chemistry (See, e.g., Figure 2, and specification page 16, paragraph 1). One of ordinary skill in the art would recognize that only routine experimentation would be needed to exploit Applicant's method for making other small molecule like compounds.

Applicant submits therefore that the breadth of the claimed method is commensurate with the disclosure and that known in the art with respect to making and using nucleic acids for selective hybridization, nucleic acid tags with different chemical reaction sites, and reactions

conditions and reagents suitable for carrying out combinatorial synthesis compatible with nucleic acids.

The Office Action at pages10-11 asserts the following regarding the state of the art / the predictability or lack thereof in the art:

> It is known in the art that certain chemical reactions would destroy the integrity of nucleic acid molecules. For example, Greene et al (Protective Groups in Organic Synthesis. 3rd ed. NY. 4/1999; p.v, pp. 1-5, p. 502-503 only) teaches "when a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked" (p. 1, lines 1+). Greene et al also teach the protection of the nitrogen bases including adenine, cytosine, etc. are needed (p. 502, last para). Thus, in chemical synthesis such as generation of oligonucleotides (i.e. addition of nucleotides to a nucleic acid strand), protection groups of the "multifunctional compounds" (such as nucleic acids) are needed to protect the integrity of the generated nucleic acids. The instant specification does not provide any guidance to the reaction condition under which the "first" and "second" or any subsequent "synthesis steps" are carried out. It is not shown how the integrity of the nucleic acids would be preserved for conducting subsequent or concurrent hybridization reactions. Furthermore, even with the appropriate protection groups such as carbamates formed on the nucleotide bases, problems such as interference with proper base pairing during hybridization reaction would still exist.

In the interest of expediting prosecution and without conceding to the correctness of this aspect of the rejection, Claim 1 has been amended to specify that the nucleic acid tag is DNA, and to clarify that the reaction steps are carried out under conditions effective to produce the desired product (e.g., see original claims 3 and 4, and specification page 15, line 34 – page 16, line 18). Claims 1 and 5 also have been amended to specify that the immobilized sequence is removed after splitting, prior to the reaction step. And the specification describes by way of example a method for carrying out such synthesis reactions on nucleic acid tags composed of DNA using compatible reagents and conditions (See, e.g., specification page 16, paragraph 1).

As noted above, one of ordinary skill would not set out to defeat the purpose of the claimed method. For instance, in possession of Applicant's specification, one of ordinary skill would not choose chemical reactions or conditions known to destroy the integrity of nucleic acids (e.g., strong acidic conditions, such as those used to remove some protecting groups from amino acids cited in Green et al, *supra*). Indeed, it was well known that a broad range of reagents

and conditions were available and suitable for carrying reactions and syntheses on, and compatible with unprotected nucleic acids (See, e.g., Chu, BC, et al. Nucleic Acids Research 11(18):6513-6529 (1983); "Oligonucleotide Synthesis: A Practical Approach", ed. M. J. Gait, JRL Press, New York, N.Y. (1990); and Green et al. *supra* and Green et al., "Protective Groups in Organic Synthesis. 2nd ed. NY 1991). See also, Famuloket al. Top. Curr. Chem. (1999) 202:101-131; Carola et al., Curr. Opin. Chem. Biol. (1999) 3:274-283; Gat et al., In *Templated Organic Synthesis* (Eds.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim 1999, pp. 133-157; Kozlov et al., J. Am. Chem. Soc. (1999) 121:5856-5859; Gat et al., Biopolymers 1998, 48:19; Luther et al, Nature (1998) 396:245-248; Liu et al., Nucleic Acids Res. 1998, 26, 3300; Schmidt et al., Nucleic Acids Res. (1997) 25:4792; Li et al., *Organic reactions in aqueous media*, Wiley, New York, 1997;. Scott, AI.,Tetrahedron Lett. (1997) 38:4961; Bruick et al., Chem. Biol. (1996) 3:49-56; Bruick et al., Chem. Biol. (1996) 3:49; Herrlein et al., J. Am. Chem. Soc. (1995) 117, 10151; Orgel, E, Acc. Chem. Res. (1995) 28:109-118) Herrlein et al., J. Am. Chem. Soc. (1995) 117:10151-10152; and Li et al., Nature (1994) 369:218). For some recent reviews, see Summerer et al., Angew. Chem. Int. Ed. (2002) 41(1):89-90; and Gartner et al., Angew. Chem. Int. Ed. (2002) 41(10): 1796-1800). The art was not unpredictable.

The Office Action at page11 also asserts the following regarding the state of the art / the predictability or lack thereof in the art:

> The instant claims also encompass attaching the "chemical reaction site" anywhere on the "nucleic acid tags". For example, a reaction moiety (such as a small organic molecule) can be attached at the middle of the hybridization sequences. It may be likely that the reaction moiety would interfere with the hybridization reaction (e.g. attachment onto the nucleotide base), or the formed hybridization complex may interfere with the chemical reaction.

Without conceding to the accuracy of the rejection and in the spirit of advancing prosecution, the claims as amended are limited to nucleic acid tags having the chemical reaction site covalently attached at the 5' terminus. The specification explains that the nucleic acid tags must be capable of hybridizing to an immobilized sequence, describes by way of example nucleic acid tags modified with a chemical reaction site at the 5' terminus suitable for this purpose (See, Figure 1). The literature was, and it replete with nucleic acid sequences suitable for this purpose (See. e.g., Abelson, J. N., Methods in Enzymology 267: 1-483 (1996); Fitzwater and Polisky, Methods Enzymol 267:275-301 (1996); Chu, BC, et al. Nucleic Acids Research

11(18):6513-6529 (1983); and "Oligonucleotide Synthesis: A Practical Approach", ed. M. J. Gait, JRL Press, New York, N.Y. (1990)). See also, Famuloket al. Top. Curr. Chem. (1999) 202:101-131; Carola et al., Curr. Opin. Chem. Biol. (1999) 3:274-283; Gat et al., In *Templated Organic Synthesis* (Eds.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim 1999, pp. 133-157; Kozlov et al., J. Am. Chem. Soc. (1999) 121:5856-5859; Gat et al., Biopolymers 1998, 48:19; Luther et al, Nature (1998) 396:245-248; Liu et al., Nucleic Acids Res. 1998, 26, 3300; Schmidt et al., Nucleic Acids Res. (1997) 25:4792; Li et al., *Organic reactions in aqueous media*, Wiley, New York, 1997;. Scott, AI.,Tetrahedron Lett. (1997) 38:4961; Bruick et al., Chem. Biol. (1996) 3:49-56; Bruick et al., Chem. Biol. (1996) 3:49; Herrlein et al., J. Am. Chem. Soc. (1995) 117, 10151; Orgel, E, Acc. Chem. Res. (1995) 28:109-118) Herrlein et al., J. Am. Chem. Soc. (1995) 117:10151-10152; and Li et al., Nature (1994) 369:218). For some recent reviews, see Summerer et al., Angew. Chem. Int. Ed. (2002) 41(1):89-90; and Gartner et al., Angew. Chem. Int. Ed. (2002) 41(10): 1796-1800.

The Office Action at page11 further asserts the following regarding the state of the art / the predictability or lack thereof in the art:

> In addition, the instant claims recite "nucleic acid tags" without specifying if the nucleic acid molecules are single stranded or double stranded. In certain method steps (e.g. Claim 10), the method requires nucleic acids to be in the double stranded form for the claimed "restriction" digestion to proceed, because "restriction enzymes" recognizes double stranded nucleic acid molecules. However, throughout the instant claims (e.g. Claim 1), the "nucleic acid tags" seem to be in single stranded forms, because the "nucleic acid tags" are hybridized to the "immobilized nucleotide sequence". Thus, for "nucleic acid tags" in the single stranded form, the instant specification has not shown possession of the method of "restriction digestion". For double stranded "nucleic acid tags", the instant specification has not shown possession of how the hybridization steps can occur.

In the interest of advancing prosecution and without conceding to the accuracy of this aspect of the rejection, Claims 1 and 5 have been amended to specify that the immobilized sequence is removed after splitting, and Claim 10 has been amended to recite a PCR amplification step.

Applicant submits that one of ordinary skill in the art would have been well aware of the conditions for nucleic acid hybridization, and that hybridization of the nucleic acid tag to the

immobilized complementary sequence could be carried out starting with either single or double stranded material using well known and routine hybridization conditions suitable for such purpose (See, e.g., Southern, EM et al., Nucl. Acids Res. 22(8) 1368-1373 (1994)).

The fact that some embodiments use double stranded material for hybridization and restriction, while others employ single stranded material would have been clear to the ordinary practitioner in reading Applicant's specification. One of skill would also recognize that it would simply be a matter of routine experimentation to generate either single stranded or double stranded material by any one of a number of known techniques and vise versa (See, e.g., Southern, EM et al., Nucl. Acids Res. 22(8) 1368-1373 (1994)).

The Office Action at pages11-12 concludes the following regarding the state of the art / the predictability or lack thereof in the art:

> The above only illustrate a few examples of how unpredictable the method of using nucleic acid molecules as tags to select or make chemical products through the entities attached to the nucleic acid tags. The instant disclosure also does not provide any structural limitation or representative species to show possession of the claimed entire genus of methods that use different reagents/compounds and steps. Although there may be suggested methods of overcoming these problems through non-routine experimentations, there are no predictable methods or solutions that would solve all the problems for any nucleic acid tags, any chemical reaction, any reaction agents, etc.

The Examiner erroneously concludes that the art is unpredictable. On the contrary, Applicant submits that the claimed method may be carried out to synthesize a broad range of compounds from their chemical subunits, ranging from relatively simple molecules such as oligomers and small organic molecules to even larger more complex molecules such as proteins. See, for example, the synthesis of polypeptides and peptide libraries (page 11, lines 13 - 17; page 15, line 27 - page 16, line 18), RNA (page 11, line 19), and "small organic molecules, polyketides, subunit oligomers and catalysts for the synthesis of complex molecules from simple substrates, e.g., transition metal mediated reactions termed 'domino' reactions which are highly efficient processes that allow for production of large libraries of complex structures in relatively few steps beginning with simple precursors. See, e.g., Titze and Lieb, *Curr Opin Chem Biol* 2:63-371 (1998)" (page 18, lines 6 - 11).

With this said, Applicant has amended the claims to limit the nucleic acid tags to DNA, the chemical reaction site to the 5' terminus, and the reagents to those that couple a chemical subunit to the tags under conditions effective to form a "different sequence oligomer or different sequence small-molecule compound" attached to a nucleic acid tag. As described in the specification, "different sequence oligomer" are oligomers, and "different sequence small-molecule compounds" are small organic molecules, both of which are representative of typical molecules found in small molecule libraries (See, specification page 7, lines 19-24, and page 9, lines 4-9).

As observed by the Examiner on page 7 of Paper No. 8, when referring to the compounds capable of being produced by the methods of instant invention, "...the state of the prior art ... is replete with numerous types of compounds synthesized and or utilized in combinatorial solid and liquid phase chemistry." Thus, the art is not unpredictable, the quantity of experimentation is standard in the art, and tag-directed synthesis of a number of compounds are described in the specification and the prior art is replete with numerous examples.

Indeed, the reaction conditions and reagents to carry out step-wise syntheses using the chemical subunits of such classes of molecules for a synthetic compound library perspective were well known as noted above, and Applicant submits that no more than routine experimentation would be required to undertake such synthesis once in possession of Applicant's disclosure. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. Id. *M.I. T.*

The Office Action at pages12 asserts the following regarding the amount of guidance present / the presence or absence of working examples:

> The instant specification is general and prophetic in nature, and does not provide any specific examples of the claimed genus of nucleic acid molecules, chemical reactions, and chemical reagents that are capable of being used with the claimed method. In particular, the specification does not demonstrate what specific nucleic acid sequences are capable of forming the "nucleic acid tags" that would hybridize for the selection steps, and also allowing the chemical reactions to proceed. The instant specification also does not provide any working examples of a chemical synthesis step performed on the claimed nucleic acid tags.

Applicant disagrees. The specification, taken in conjunction with the teachings of the prior art, provide a great deal of guidance as to how to practice the claimed method, including making and using nucleic acid molecules, chemical reactions, and chemical reagents.

Nevertheless, in the interest of expediting prosecution and without conceding to the accuracy of the rejection, Claim 1 and the relevant dependent claims are amended to specify that the hybridization sequences are "variable" hybridization sequences capable of "specific hybridization" to a corresponding immobilized sequence. For example, the specification clearly describes that a "variable" hybridization sequence refers to the hybridization sequences which are different for each group of subsets of nucleic acid sequences (e.g., specification page 12, lines 31-32), and "specific hybridization" refers to temperature, ionic strength and/or solvent conditions effective to produce sequence-specific pairing between a single-stranded oligonucleotide and its complementary-sequence nucleic acid strand, for a given length oligonucleotide (e.g., specification page 7, lines 25-28). Multiple sequences suitable for this purpose were known or could have been be routinely constructed (See. e.g., Abelson, J. N., Methods in Enzymology 267: 1-483 (1996), and Fitzwater and Polisky, Methods Enzymol 267:275-301 (1996); see also, above-cited references)

Regarding sequences that would hybridize for the reaction steps, again, in the interest of expediting prosecution and without conceding to the correctness of this aspect of the rejection, Claims 1 and 5 have been amended to clarify that the selected hybridization complexes are physically separated from each other and that the immobilized sequence is removed prior to the reaction step.

As to working examples, the specification discloses nucleic acid tags that exemplify those suitable for carrying out the claimed method (e.g., Figure 1), as well as use of the tag-directed synthesis of peptides with compatible reagents and conditions illustrated by well known Fmoc chemistry (See, e.g., Figure 2, and specification page 16, paragraph 1). One of ordinary skill in the art would recognize that only routine experimentation would be needed to exploit Applicant's method for making and using the invention without undue experimentation.

For instance, Applicant submits that one of ordinary skill in the art would have clearly recognized that the reagents and conditions that could be exploited in Applicant's method for coupling to nucleic acids without impacting hybridization or allowing synthesis to proceed. (See, e.g., Corey et al., Bioorganic Chemistry Frontiers 2:1-31 (1999); Pei et al., PNAS (1990),

87(24):9858-62; Corey et al., J. Amer Chem Soc (1989) 111(22):8523-5; Corey et al., Biochemistry (1989) 28(21):8277-86; Corey et al., J Biol Chem (1989) 264(7):3666-9; Zuckermann et al., J Amer Chem Soc (1988) 110(5):1614-15; and Corey et al., Science (1987) 238(4832):1401-3; Famuloket al. Top. Curr. Chem. (1999) 202:101-131; Carola et al., Curr. Opin. Chem. Biol. (1999) 3:274-283; Gat et al., In *Templated Organic Synthesis* (Eds.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim 1999, pp. 133-157; Kozlov et al., J. Am. Chem. Soc. (1999) 121:5856-5859; Gat et al., Biopolymers 1998, 48:19; Luther et al, Nature (1998) 396:245-248; Liu et al., Nucleic Acids Res. 1998, 26, 3300; Schmidt et al., Nucleic Acids Res. (1997) 25:4792; Li et al., *Organic reactions in aqueous media*, Wiley, New York, 1997;. Scott, AI.,Tetrahedron Lett. (1997) 38:4961; Bruick et al., Chem. Biol. (1996) 3:49-56; Bruick et al., Chem. Biol. (1996) 3:49; Herrlein et al., J. Am. Chem. Soc. (1995) 117, 10151; Orgel, E, Acc. Chem. Res. (1995) 28:109-118) Herrlein et al., J. Am. Chem. Soc. (1995) 117:10151-10152; and Li et al., Nature (1994) 369:218). For some recent reviews, see Summerer et al., Angew. Chem. Int. Ed. (2002) 41(1):89-90; and Gartner et al., Angew. Chem. Int. Ed. (2002) 41(10): 1796-1800).

The Office Action at pages12-13 asserts the following regarding the quantity of experimentation needed:

> Due to the unpredictabilities of various chemical reactions performed on nucleic acid tags (and/or its linked chemical reaction sites) and the effects of the chemical reactions on the hybridization of the nucleic acid tags, undue experimentation would be required. The art has not demonstrated all the possible nucleic acid tags and all possible chemical reactions that are compatible with the linked nucleic acid tags. Because the instant specification does not provide any specific guidance on how various chemical reactions can be conducted without destroying the integrity of the nucleic acid tags and other problems associated with the claimed method, undue experimentation would be required to practice claimed method of synthesizing any chemical compound using any linking nucleic acid tags.

Applicant disagrees. As observed by the Examiner on page 7 of Paper No. 8, when referring to the compounds capable of being produced by the methods of instant invention, "...the state of the prior art ... is replete with numerous types of compounds synthesized and or utilized in combinatorial solid and liquid phase chemistry." Thus, the art is not unpredictable, the quantity of experimentation is standard in the art, and tag-directed synthesis of a number of

compounds are described in the specification and the prior art is replete with numerous examples.

As noted above, the specification discloses nucleic acid tags illustrative of those suitable for carrying out the claimed method (e.g., Figures 1 and 2, and specification page 16, paragraph 1). One of ordinary skill in the art would recognize that only routine experimentation would be needed to exploit Applicant's method for making and using the invention without undue experimentation.

As also noted above, it was well known that a broad range of reagents and conditions were available and suitable for carrying reactions and syntheses on, and compatible with protected or unprotected nucleic acids.

The Office Action at page13 concludes with the following assertion:

> Due to the non-routine experimentation necessary to determine the specific methods for conducting chemical synthesis using chemical reaction sites linked to nucleic acid tags while allowing specific hybridization to occur prior, during or subsequent to the chemical reactions; the lack of direction/guidance presented in the specification regarding the specific requirements for the method; the unpredictability of various chemical syntheses using compounds with multifunctional groups (such as nucleic acids) as established by the state of the prior art; the breadth of the claims, undue experimentation would be required of a skilled artisan to make and/or use the claimed invention in its full scope.

Applicant submits that even though a large number of possible compounds and syntheses using the claimed methods are encompassed by the claims, this factor is not determinative. As stated above, the standard for § 112 enablement is that one skilled in the art would have been able to use the description of the invention to make and use the claimed invention without undue experimentation. Complex experimentation does not make it undue, if the art typically engages in such experimentation. See M.I.T., *supra*.

One skilled in the art would understand this method to be a process that will work with a wide variety of compounds synthesized and/or utilized in combinatorial chemistry, particularly oligomers and small organic molecules as currently claimed. As regards the state of the prior art, both solid and liquid phase combinatorial chemistry methods were well known, and were

routinely being applied to a broad range of protected or unprotected nucleic acids for synthesis and hybridization. Thus, a great deal was known about synthesizing compounds in a combinatorial manner. The Examiner also agrees that the relative skill of those in the art is quite high, most likely at the Ph.D. level. The breadth of the current claims also clearly supports a finding of enablement. The claims require the synthesis of a plurality of compounds utilizing nucleic acid tags that have hybridization sequences and chemical reaction sites, each of which have been defined appropriately.

Accordingly, Applicant submits that the specification fully enables one skilled in the art to carryout the present invention without undue experimentation, thereby satisfying the requirements of 35 U.S.C. § 112, first paragraph.

In view of the foregoing remarks, Applicants respectfully that the rejection of Claims 1, 3-10, 15 and 16 under 35 U.S.C. §112, first paragraph be withdrawn.

**REJECTIONS UNDER §112, ¶2**

Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each aspect of the rejection is reiterated below, followed by Applicant's response.

The Office Action at page 14 asserts the following:

> **A.)** Claim 1 method recites the method step of "(a) forming a first group of subsets of nucleic acid tags ... by hybridization between one of said first hybridization sequences and the first immobilized sequences", which can be interpreted to mean that hybridization complexes have been formed between the tags and the immobilized nucleic acids. The claim also recites a step "(b) carrying out the first synthetic step ... of the subsets formed in (a)", which can be broadly interpreted to mean the reactions are conducted using the hybridization complexes formed in step (a) of Claim 1. That is the hybridization complexes are maintained while allowing the chemical reaction to occur. However, applicants in the Reply (entered 12/4/06; p. 7) seem to argue that claim should be interpreted to mean that the hybridization complexes occur at different time from the chemical reactions. Applicants' narrow interpretation seems to be in conflict with the broad and reasonable interpretation of the instant claim language. Thus, applicants invention are not clearly described by the instant claim language. One of skill in the art would not be able to define the metes and bounds of the instant claimed invention.

Applicant disagrees. Applicant's comments in the subject Reply were made in the context of the specific references being discussed. The comments were made to point out that the hybridization reaction of step (a) occurs before the chemical reaction of step (b), and thus the hybridization conditions for step (a) were irrelevant for the chemical reaction conditions of step (b). There is nothing inconsistent about this statement. The claim and specification clearly indicate that the hybridization complexes are first captured as subsets in step (a), and that the chemical reaction is then carried out on those subsets in step (b).

In the interest of expediting prosecution and without conceding to the correctness of this aspect of the rejection, Clam 1 has been amended to clarify that the captured subsets are physically separated from each other prior to chemical transformation step.

The Office Action at page 14 asserts the following:

> **B.)** Claim 5 recites the limitation "the compound intermediates" in step (g). There is insufficient antecedent basis for this limitation in the claim.

Claim 5 is amended to recite "reagent-specific compound intermediates" to provide for antecedent basis.

The Office Action at page 14 asserts the following:

> C.) Claim 16 recites the limitation "the separate subset" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 16 is amended to recite "reagent-specific compound intermediates" to provide for antecedent basis.

The Office Action at page 14 asserts the following:

> D.) Claim 9 recites "wherein said using includes", which the term said using is not clear. It is not clear if claim 9 is reciting a subsequent method step following the method steps recited in Claim 8, or if claim 9 is further limiting the method steps recited in Claim 8.

In the interest of expediting prosecution and without conceding to the correctness of this aspect of the rejection, Clam 9 has been amended to clarify the term "using" by deleting the phrase "using said amplified subpopulation having chemical reaction sites to carry out the method of claim 1."

The Office Action at pages 14-15 asserts the following:

> E.) Claim 10 recites the limitation "said plurality of compounds" in step (f). There is insufficient antecedent basis for this limitation in the claim. It is not clear to which one of the "compounds" recited in the preamble of Claim 10, the compound intermediate of Claim 1, and the final compounds formed in Claim 1.

In the interest of expediting prosecution and without conceding to the correctness of this aspect of the rejection, Clam 1 is amended to recite "whereby a plurality of compounds is produced" at the end of step (f) for antecedent basis for claim 10.

The Office Action at page 15 asserts the following:

> F.) The claim language of 10 is convoluted and confusing. It is not clear if the recited method steps (f)-(i) are further limiting the recitation of Claim 7 or the steps are further method steps comprised by the method of claim 1.

In the spirit of providing clarity to the claim and without conceding as to the correctness of the rejection, Claim 10 has been amended to specify that the steps are further method steps.

In view of the above remarks and amendments, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

**REJECTIONS UNDER §102**

***Legal standard***

It is well settled that in making out a *prima facie* case of anticipation under §102, each and every element of the claimed invention, arranged as required by the claims, must be found in a single prior art reference, either expressly or under the principles of inherency. See generally *In re King*, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986); *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1458, 221 USPQ 481, 485 (Fed. Cir. 1984). Thus for a reference to anticipate, it must disclose each and every feature of the claimed invention as a whole. Piecemeal construal of a reference is inappropriate: one is not free to pick and choose among dissected parts of a reference, and then recombine them in a manner contrary to the disclosure of that reference.

***Claim amendments***

In the interest of expediting prosecution and without conceding to the correctness of the rejections addressed below, Applicant has clarified that the method of base Claim 1 involves, in general, the following series of steps:

(a) providing a pool of subsets of nucleic acid tags,

(b) splitting the pool of nucleic acid tags of step (a) to form a first group of subsets of nucleic acid tags for participating in a first synthetic reaction,

(c) carrying out the first synthetic reaction by reacting the chemical reaction sites of the nucleic acid tags in each of the subsets formed in step (b),

(d) pooling the first group of subsets of reacted nucleic acid tags of step (c) to form a first pool of reacted nucleic acid tags,

(e) splitting the first pool of reacted nucleic acid tags of step (d) to form a second group of subsets of reacted nucleic acid tags for participation in a second synthetic reaction step, and

(f) carrying out the second synthetic reaction by reacting the reagent-specific compound intermediate of the reacted nucleic acid tag in each of the subsets formed in step (e).

Claim 1 (and Claim 5) has also been amended to clarify the nature of the nucleic acid tag subsets and pools that contain them. In particular, the amendment clarifies that each pool contains subsets of nucleic acid tags with different nucleotide sequences, by specifying that the variable hybridization sequences are different for each subset of tags (and thus each pool from which a subset is derived contains a mixture of different tags with different variable hybridization sequences).

***Brenner (US 5,635,400)***

Claims 1, 3-8, 10, 15 and 16 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Brenner (US 5,635,400; 6/3/1997). The rejection is avoided in part and traversed in part for the reasons that follow.

The Office Action at pages 16 -18 asserts the following:

> Brenner, throughout the patent, teaches using various methods of using oligonucleotide tags.
>
> The reference teaches generating a variety of oligonucleotide tags with attached "reactive functionalities (e.g. col. 9, lines 15+) and various hybridization sequences (e.g. col. 6+), which read on the "nucleic acid tags" linked to a chemical reaction site of **clm 1**.
>
> The reference teaches hybridizing the "oligonucleotide tags" to a solid support through its complementary hybridization sequences (e.g. col. 12, lines 15+; Figure 4, where the solid support (245) has immobilized hybridization nucleotide sequences (250) that are complimentary to the olignucleotide tags (255)), which reads on the **(a) of clm 1**, and the solid support of **clm 15**.

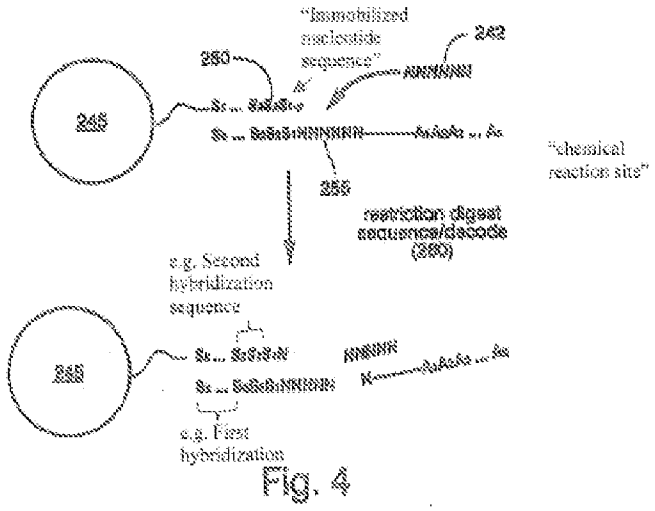


Fig. 4

> The reference also teaches attaching various moieties to the end of the oligonucleotide tags (e.g. col. 9) through chemical reactions such as synthesizing labeled peptides (e.g. cols. 11-12; top of Figure 4), and restriction digestion of the hybridized oligonucleotide tags (e.g. col. 12, lines 15+), which either the chemical reactions or the restriction digestion reads on **(b) of clm 1**.

First, the fact that Brenner discloses oligonucleotide tags, tags attached to various reactive functionalities, attaching them to various moieties, tags with restriction sites, and sequencing the tags is not dispositive of anticipation of Applicant's method. That bits and pieces of Applicant's method may be scattered throughout Brenner is irrelevant. Nowhere does Brenner disclose (expressly or inherently) any method specifying steps (a) – (f) as in Claim 1, much less the method of Claim 1 which is further limited to specific embodiments as in Claims 3-10 and 15-16.

Brenner's method of making a plurality of oligonucleotide-tagged compounds involves: (i) carrying out a 'sequential encoding' process for making oligonucleotide-tagged compounds in which synthesis of the compound library involves alternate additions of a nucleic acid sequence "$S_k$" with compound monomers "$A_k$" to generate a library of oligonucleotide-tagged compounds, followed by (ii) screening the tagged compounds to select tagged compounds having a desired activity, followed by (iii) sorting the tagged compounds having a desired activity, followed by (iv) sequencing the tagged compounds of interest using a single base DNA sequencing method to identify the library compound (see, e.g., Brenner Figure 4, and column 11, line 25 – column 12, line 25).

As can be appreciated, Brenner's method for making tagged-compound libraries differs markedly from Applicant's method. Brenner discloses a 'sequential encoding' process for making compounds in which each chemical transformation step on the tag requires that it is carried out concurrent with the physical addition of a new nucleic acid sequence to the tag. Specifically, Brenner discloses a sequential encoding method in which "Synthesis proceeds by successive alternative additions of subunits $S_1$, $S_2$, $S_3$, and the like, to form the tag 212 and their corresponding library compound monomers." (See Brenner Figure 4, and at column 11, line 65 through column 12, line 2). Thus, Brenner's method involves successive alternative additions of a nucleic acid subunit "$S_k$" at each corresponding chemical synthesis step "$A_k$", which is used to report the sequence of reactions that have been carried out, allowing the identification of the molecule based on its synthetic history.

In contrast, Applicant's claimed method employs 'pre-encoded' nucleic acid tags in step (a) that require absolutely no further nucleic acid sequences be added or removed when used to carry out steps (b) – (e) (now steps (b) – (f) as amended) in making a plurality of compounds per Claim 1. All of the information for the synthesis and final synthesis product is pre-encoded in each nucleic acid tag of Applicant's method. In other words, in Applicant's method, the variable hybridization regions that dictate a given hybridization-based splitting of a pool of tags into subsets (or sub-pools) are already present in the tag, and it is the hybridization split that dictates and directs what chemical reaction is carried out on that tag in the next synthetic step, and <u>not</u> the addition of a new nucleotide sequence to the tag at each synthetic step as required by Brenner.

Thus, such nucleic acid tags <u>when employed in a method as specified to be carried out according to Claim 1</u> not only encode a compound to which it is attached (i.e., compound

identity), they actually direct synthesis of the compound by routing the nucleic acid tag (or tagged compound intermediate) to a specific sub-pool (via the hybridization-split) where a selected synthesis reaction is then carried out on the tag, as opposed to merely reporting on the synthetic history of a compound as with Brenner.

Second, the screening, sorting and sequencing aspects of Brenner's method add nothing. In particular, Applicant understands the main thrust of the rejection to be based on the single base DNA sequencing method of Brenner. In particular, "Fig.4" depicted in the Office Action is only a portion of actual Figure 4 of Brenner, with annotations by the Examiner, and which portion only refers to the single base DNA sequencing step of Brenner.

The single base DNA sequencing process of Brenner is carried out on a single nucleic acid species by a sequential, single base extension /reading process (see, e.g., Brenner Figure 4, and column 12, lines 21-24). Applicant's method is not drawn to a sequencing method, and would not be suited as a sequencing method at all given the simple fact that is carried out on a mixed population of nucleic acid tags with different sequences (which is clarified by the current amendment).

For instance, Brenner's sequencing method requires that the sequencing process be carried out on a single template, with no mixing of that species with others having different sequences at any time in the process. To do so would destroy the purpose of Brenner's sequencing method by mixing signal output from one species with another, with no possibility of deciphering what signal came from which sequence. Even a single pooling of different template sequences from one extension reaction and then splitting them based on a completely different template sequence before carrying out a next sequencing reaction using Brenner's sequencing method would result in garbled output.

This is in contrast to Applicant's method which requires at least one round of pooling, splitting, and reacting be carried out on a mixed population of previously reacted nucleic acid tags with different sequences.

Further, the nucleotide extension reaction of Brenner's single base DNA sequencing method involves ligation of the splint and single base extension at the 3' terminus of the immobilized sequence (e.g., see Brenner, Figure 1c), and not the 5' terminus of the tag as required in Claim 1 as amended.

For these reasons alone, Applicant submits that Brenner fails to anticipate the method according to Claim 1 as a whole, much less the method according to Claims 3-10 and 15-16, and respectfully requests that the rejection be withdrawn.

Lastly, Applicant also notes that the Office Action mischaracterizes Brenner and Applicant's claimed method in an inappropriate attempt to apply disjointed fragments of Brenner's disclosure against various other specific steps of Claim 1, and the dependent Claims 3-10 and 15-16. Each aspect of this part of the rejection is reiterated below.

The Office Action at page 17 asserts the following:

> The reference teaches sorting the oligonucleotides (e.g. col. 12, lines 10+), which reads on **(c) of clm 1**.

First, this aspect of the rejection is irrelevant as Brenner fails to disclose the method of Claim 1 as a whole. Second, Applicant disagrees with the Examiner's characterization of step (c) of Claim 1 (now step (d) as amended) with respect to Brenner. Referring to Figure 4 of Brenner, the "sorting" step (240) at column 12 lines 10+ of Brenner does not involve pooling as required by step (c) of Claim 1 (now step (d) as amended).

The Office Action at page 17 asserts the following:

> As indicated in Figure 4 cited above, the reference also teaches a second hybridization sequence that are hybridized to the a second immobilized nucleotide sequence (e.g. Figure 4), which reads on **(d) of clm 1**.

First, this aspect of the rejection is irrelevant as Brenner fails to disclose the method of Claim 1 as a whole. Second, the Examiner assertion with respect to step (d) (now step (e) as amended) is inaccurate. The ligation step of Brenner noted in the modified Figure 4 of the Office Action employs hybridization of a non-variable splint to a non-variable sequence. In contrast, Step (d) of Claim 1 (now step (e) as amended) requires a second immobilized sequence hybridize to one of the second variable hybridization sequences of the nucleic acid tag. Nowhere does Figure 4 of Brenner disclose this.

The Office Action at page 18 asserts the following:

> The reference also teaches ligating another nucleotide sequence to the restricted oligonucleotide tag during the "single base DNA sequencing" procedure (e.g. cols. 16-17; especially, col. 16, lines 65+; Figures 1 and 2), which reads on **(e) of clm 1**.

This aspect of the rejection is irrelevant as Brenner fails to disclose the method of Claim 1 as a whole. Applicant also notes that, as currently amended, the synthetic step (e) (now step (f) as amended) of Claim 1 involves synthesis from the 5' terminus, not the 3' terminus according to the ligating and single base DNA sequence procedure of Brenner.

The Office Action further has rejected claims 3-10 and 15-16 that depend from Claim 1 as being anticipated by Brenner for various reasons, each of which rejections is reiterated below

The Office Action at page 18 asserts the following:

> The "restriction" and "ligation" reactions taught by the reference either cuts or adds nucleotides to the oligonucleotide tags (or nucleic acid tags), which reads on the "different oligomer subunits" of **clm 3**, as well as the "different compound substituents" of **clm 4**.

First, this aspect of the rejection is irrelevant as Brenner fails to disclose the method of Claim 1 as a whole, and thus Claims 3 and 4 which further limit Claim 1. Second, Applicant disagrees with the Examiner's characterization of Brenner, which discloses carrying out restriction and ligation on a single oligonucleotide tag species, not a plurality as required by Claims 3 and 4. Furthermore, as currently amended, the claims require synthesis occur from the 5' terminus of the tag, not the 3' terminus according to the ligating and single base DNA sequence procedure of Brenner.

The Office Action at page 18 asserts the following:

> The reference also teaches repeating the ligation, restriction cleaving, identifying, etc., (reads on the hybridization and the synthetic step discussed above) for as many times as necessary (e.g. col. 17, lines 4+), which reads on the "N" synthetic steps of **clm 5**, the iterative step of **clm 8**, and the method steps of **clm 10**.

First, this aspect of the rejection is irrelevant as Brenner fails to disclose the method of Claim 1 as a whole, and thus Claims 5, 8 and 10 which further limit Claim 1. Second, Applicant disagrees with the Examiner's characterization of Claims 5, 8 and 10 with respect to Brenner. The Brenner reference at column 17, lines 4+ refers to the single base DNA sequencing procedure that is carried out on a single nucleic acid species. Nowhere does Brenner disclose iterative rounds of forming pools of different tags, much less splitting by hybridization and carrying out synthesis on each subset of tags generated by such pooling and hybridization-based splitting (Claim 5). As noted above, Brenner's sequencing method would be rendered inoperable

if carried out recombining mixtures of different sequences and then splitting the mixtures based on a completely different sequence before carrying out the next single base sequencing step – such an approach would generate non-interpretable sequencing information. For the same reason, Brenner does not disclose carrying out the method of Claim 1 on a subpopulation of different tags as required by Claims 8 and 10.

The Office Action at page 18 asserts the following:

> The reference teaches each oligonucleotide tag has different subset of sequences (e.g. Figure 4; cols. 6-7+), and each of the ligation step during the "single base DNA sequencing" also produce different sequences for the oligonucleotide tags (e.g. col. 17-18), which reads on the at least 5 separate hybridization sequences of **clm 6**.

This aspect of the rejection is irrelevant as Claim 6 further limits the tags employed in the method of Claim 1, and Brenner does not disclose a method according to Claim 1 as a whole. Furthermore, columns 6-7 of Brenner disclose a method for designing minimally cross-hybridizing tags, and not a method for making a plurality of compounds according to Claim 1, or such as method carried out with a nucleic acid tag having at least 5 separate variable hybridization sequences as required by Claim 6.

The Office Action at page 18 asserts the following:

> The reference teaches a restriction site in the oligonucleotide tags (e.g. Figure 4, the "NNNNN" region; col. 11, lines 60+), and the oligonucleotides having "sets" of sequence that are the same (e.g. col. 6, lines 30+), which reads on the "spacer sequence" of **clm 7**, and the restriction sites of **clm 10**.

This aspect of the rejection also is irrelevant as Brenner fails to disclose the method of Claim 1 as a whole, and thus such a method as further limited by Claims 7 and 10. In addition, the "NNNNN" restriction site in Figure 4 and column 11, lines 60+ does not separate first and second variable hybridization sequences at all; the "NNNNN" restriction site sequence in Figure 4 of Brenner has only the "Sk…$S_3S_2S_1$" nucleotide sequence on one side. In contrast, Claim 7 requires that the first and second variable hybridization sequences are separated by a spacer sequence, and thus claim 10 requires that the restriction site be flanked by first and second hybridization sequences as well. Furthermore, as amended, Claim 7 clarifies that that the spacer

sequence is a constant spacer sequence, not a variable sequence. Brenner is completely devoid of disclosing constructs of this nature, much less there use in the method of Claim 1.

The Office Action at page 18 asserts the following:

> The reference teaches sorting the oligonucleotide tags into tubes, or other solid substrate (e.g. cols. 19-20), which reads on the limitation of claim 16.

First, this aspect of the rejection is irrelevant as Brenner fails to disclose the method of Claim 1 as a whole, and thus such a method as further limited by Claim 16. Second, Applicant disagrees with the Examiner's characterization of Brenner and Claim 16. Brenner at columns 19-20 refers again to generating single species of tags for single base DNA sequencing. Brenner does not disclose any recombination of the different sequences in a pooling step and subsequent splitting for directing the next synthetic step, such as required by Claim 16 given its dependence from Claim 1; otherwise Brenner's sequencing method would be rendered unworkable as discussed above.

In view of the above remarks, Applicant respectfully request that the rejection of Claims 1, 3-8, 10, 15 and 16 under 35 U.S.C. 102(b) as being anticipated by Brenner be withdrawn.

***Rosenthal et al. (WO 9321340)***

Claims 1, 3-8, 15 and 16 are rejected under 35 U.S.C. §02(b) as being anticipated by Rosenthal et al (WO9321340). The rejection is avoided in part and traversed in part for the following reasons.

The Office Action at pages 19-20 asserts the following:

> Rosenthal et al, throughout the publication, teach using immobilized template and template specific primer for DNA sequencing reaction (Abstract).
>
> The reference teaches immobilizing single-stranded template (nucleic acids) to solid-phase support (pp. 7-8), which reads on the "immobilized nucleotide sequence" of step (a) of **clm 1**, as well as **clm 15**
>
> The reference teaches hybridizing a "primer" to the immobilized template (p. 7, lines, 7+ and 25+), which the primer reads on the "nucleic acid tag" of **clm 1**.
>
> The reference teaches "extending the primer by the addition of a single labeled nucleotides (p. 7, lines 10+), which reads on the "first synthetic step" of **clm 1**.
>
> The primers and the templates taught by the reference comprise at least "a first hybridization sequence" (partial sequence of the primer or the template) and "a second hybridization sequence" (partial sequence of the primer or the template), as recited in **clm 1**. The primers would also possess at least five partial sequences, which reads on the 5 separate hybridization sequences of **clm 6**, as well as the same spacer regions of **clm 7** (see also p. 24, Example 1).
>
> The primers are used in one sequencing reaction described by the reference (p. 7) would "pooled" as recite din step (c) of **clm 1**.
>
> The reference teaches repeating the extension steps of the sequence reaction while the primers are hybridized to the template (p. 7), which reads on the second hybridization step and the second synthetic reaction step of **clm 1**, as well as the N synthetic steps of **clm 5**.

Rosenthal discloses a method for sequencing DNA that involves the following steps: (a) forming a single stranded template comprising the nucleic acid to be sequenced; (b) hybridizing a primer to the template to form a template/primer complex; (c) extending the primer by the addition of a single labeled nucleotide; (d) determining the type of labeled nucleotide added onto the primer; (e) removing or neutralizing the label; and (f) repeating steps (c) to (e) sequentially and recording the order of incorporation of labeled nucleotides (See, e.g., Rosenthal Abstract, page 7, and pages 22-61 - the Examples).

Nowhere does Rosenthal disclose method specifying steps (a) – (f) as in Claim 1 as a whole, much less the method of Claim 1 which is further limited to specific embodiments as in

Claims 3-10 and 15-16.. In fact, Rosenthal fails to disclose any method that employs any nucleic acid that involves a pool-split-synthesis etc. strategy of any type. It is simply not there.

Even if one were to entertain the logic of the Office Action in citing Rosenthal, it is readily apparent that the sequencing method of Rosenthal as applied in the rejection would be rendered unworkable. For instance, the Rosenthal method requires use a single template nucleic acid for sequencing to work. As with Brenner's sequencing method discussed above, even a single pooling of different template sequences from a first extension reaction (or primers for that matter) and then splitting them based on a completely different sequence before carrying out a next sequencing reaction using Rosenthal's sequencing method would result in non-interpretable output.

Accordingly, for the above reasons alone, Applicant submits that Rosenthal fails to anticipate the method according to Claim 1, and thus cannot anticipate dependent method Claims 3-10 and 15-16, and respectfully requests that the rejection be withdrawn.

Applicant also notes that the Office Action applies fragments of Rosenthal's disclosure against dependent Claims 3-8 and 15-16, which are each addressed in the remarks that follow.

With respect to Claims 3 and 4, the Office Action at page 20 asserts the following:

> The reference teaches adding different nucleotides to the primers (pp. 11-12), which reads on the different oligomer subunits of **clm 3**, as well as the different compound substituents of **clm 4**.

This aspect of the rejection is irrelevant as Brenner fails to disclose the method of Claim 1 as a whole, and thus does not disclose such a method that is further limited to specific embodiments as in which different oligomers subunits (Claim 3) or different compound substituents (Claims 4) are employed.

With respect to Claim 5, on page 20 of the Office Action, it is asserted that Rosenthal "teaches repeating the extension steps of the sequence reaction while the primers are hybridized to the template (p. 7), which reads on the second hybridization step and the second synthetic reaction step of clm 1, as well as the N synthetic steps of clm 5." This aspect of the rejection is irrelevant as Rosenthal fails to disclose the method steps of Claim 1 as a whole for the reasons discussed above, and thus does not anticipate such a method in which making a plurality of compounds by carrying out "N" synthetic steps as required by Claim 5.

Regarding Claims 6 and 7, on page 19 of the Office Action, it is asserted that "The primers would also possess at least five partial sequences, which reads on the 5 separate hybridization sequences of cm 6, as well as the same spacer regions of clm 7 (see also p. 24, Example 1)." This aspect of the rejection is irrelevant as Rosenthal fails to disclose the method steps required by Claim 1 as a whole for the reasons discussed above, and thus does not anticipate such a method in which each subset of nucleic acid tags includes at least 5 separate hybridization sequences as required by Claim 6, or such as method in which each nucleic acid tag further comprises the adjacent spacer sequence as required by Claim 7.

Concerning Claim 8, the Office Action at page 20 asserts the following:

> The reference teaches identifying the sequence of the extended primer based on the different labels (p. 7, lines 14+), which reads on identifying a subpopulation of **clm 8** because only the right primer-template complex can produce a primer extension product.

This aspect of the rejection is irrelevant as Brenner fails to disclose the method of Claim 1 as a whole, and thus does not anticipate such a method which further requires identifying a desired activity of one or more different compounds produced by the method, and then generating a subpopulation of nucleic acid tags therefrom, and then using the subpopulation to reiterate the method as per Claim 8.

With respect to Claim 15, on page 19 of the Office Action, it is asserted that Rosenthal "teaches immobilizing single-stranded template (nucleic acids) to solid phase support (pp. 7-8), which reads on the "immobilized nucleotide sequence" of step (a) of clm 1, as well as Claim 15." This aspect of the rejection is moot as Rosenthal fails to disclose the recited method steps of Claim 1 as a whole for the reasons discussed above, and thus does not anticipate such a method in which the first and second immobilized nucleotide sequences are each bound to the surface of a solid support as required by Claim 15. In fact, no where does Rosenthal disclose a method in which first and second immobilized nucleotide sequences according to Claim 1 are each bound to the surface of a solid support as per Claim 15.

Concerning Claim 16, the Office Action at page 20 asserts the following:

> Because the sequencing reactions are carried out in test tubes (pp. 23-24), the reference's teaching reads on the limitation of **clm 16**.

This aspect of the rejection is moot as Rosenthal fails to disclose the method steps of Claim 1 explicitly or inherently as a whole, and thus does not anticipate such a method in which

the subsets of nucleic acid tags are transferred to a solid support prior to each synthetic transformation step in step as required by Claim 16.

In view of the above remarks, the rejection of Claims 1, 3-8, 15 and 16 under 35 U.S.C. §02(b) as being anticipated by Rosenthal is requested to be withdrawn.

**REJECTIONS UNDER §103(A)**

***Legal standard***

In order to establish a *prima facie* case of obviousness, both the suggestion and the reasonable expectation of success must be found in the prior art and not in applicants disclosure. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Thus, a *prima facie* case of obviousness requires showing some objective teaching or suggestion in the applied prior art taken as a whole would have led that person to the claimed invention, including each and every limitation of the claim as a whole, without recourse to the teachings in applicant's disclosure. See generally In re Oetiker, 977 F.2d 1443, 1447-48, 24 USPQ2d 1443, 1446-47 (Fed. Cir. 1992) (Nies, J., concurring); In re Fine, 837 F.2d 1071, 1074-76, 5 USPQ2d 1596, 1598-1600 (Fed. Cir. 1988); In re Dow Chem. Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988).

It is also well settled that in order to establish a *prima facie* case of obviousness based on a combination of elements disclosed in the prior art, the Examiner must articulate the basis on which she concludes that it would have been obvious to make the claimed invention. *In re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998) at 1357-59. In practice, this requires that the Examiner "explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious." *Rouffett*, 149 F.3d. at 1357-59.

***Claim amendments***

In the interest of expediting prosecution and without conceding to the correctness of the rejections addressed below, Applicant has clarified that the method of base Claim 1 involves, in general, the following series of steps:

(a) providing a pool of subsets of nucleic acid tags,

(b) splitting the pool of nucleic acid tags of step (a) to form a first group of subsets of nucleic acid tags for participating in a first synthetic reaction,

(c) carrying out the first synthetic reaction by reacting the chemical reaction sites of the nucleic acid tags in each of the subsets formed in step (b),

(d) pooling the first group of subsets of reacted nucleic acid tags of step (c) to form a first pool of reacted nucleic acid tags,

(e) splitting the first pool of reacted nucleic acid tags of step (d) to form a second group of subsets of reacted nucleic acid tags for participation in a second synthetic reaction step, and

(f) carrying out the second synthetic reaction by reacting the reagent-specific compound intermediate of the reacted nucleic acid tag in each of the subsets formed in step (e).

Claim 1 (and Claim 5) has also been amended to clarify the nature of the nucleic acid tag subsets and pools that contain them. In particular, the amendment clarifies that each pool contains subsets of nucleic acid tags with different nucleotide sequences, by specifying that the variable hybridization sequences are different for each subset of tags (and thus each pool from which a subset is derived contains a mixture of <u>different</u> tags with different variable hybridization sequences).

***Brenner in view of Lerner***

Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Brenner (US 5,635,400; 6/3/1997, herein "Brenner"), in view of Lerner et al (US 5,723,598; 3/3/1998; filing date: 6/18/1996, herein "Lerner"). The rejection is avoided in part and traversed in part for the following reasons.

The specifics of the rejection are reiterated below from page 21 of the Office Action:

Brenner, throughout the patent, teaches using various methods of using oligonucleotide tags, as discussed above.

Brenner et al do not explicitly using PCR to amplify the nucleic acid tags, as recited in clm 9.

However, Lerner et al, teach using PCR to amplify nucleic acids. The reference teaches amplification of selected DNA using PCR (col. 2, lines 22+). The reference also teaches the advantage of PCR such as allowing "serial enrichment" and subsequent sequencing step of the PCR products (col. 2, lines 22+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to amplify the selected nucleic acid tags using PCR.

A person of ordinary skill in the art would have been motivated at the time of the invention to use PCR to amplify the selected nucleic acid tags, because the advantage of the PCR technology such as allowing serial enrichment of the nucleic acid molecule and subsequent sequencing step, as taught by Lerner et al.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications, because the using PCR to amplify nucleic acid molecules is routine and known in the art as taught by both Brenner et al (col. 2, lines 22+), and Lerner et al.

It is noted that the Examiner has only articulated a basis for the rejection of Claim 9. Id. *Rouffett*, 149 F.3d. at 1357-59. Applicant respectfully submits that no *prima facie* case of obviousness has been established, as the Examiner has articulated no basis for the rejection against the parent claims from which Claim 9 depends. Nevertheless, in the interest of expediting prosecution, Applicant respectfully submits that the Brenner taken in view of Lerner would not have rendered obvious the method of Claim 1 or such a method as further limited in dependent Claims 3-9, 10 and 15-16, and in particular the method of Claim 9.

Claim 9 depends from Claim 8, and Claim 8 from Claim 1. Thus Claim 9 includes all of the limitations of its predecessor claims. The question of obviousness turns, therefore, on a method according to Claim 1 that further includes the additional steps of: (i) identifying from the plurality of compounds in step (f) of Claim 1, one or more compounds having a desired activity to yield a subpopulation of nucleic acid tags, (ii) amplifying the subpopulation of nucleic acid

tags by polymerase chain reaction (PCR), and adding a chemical reaction site, and (iii) using the amplified subpopulation of nucleic acid tags to carry out the method of Claim 1.

Neither Brenner nor Lerner teach or suggest using any nucleic acid tag a method of making a plurality of compounds according to steps (a)-(f) of Claim 1, much less using PCR to amplify a subpopulation of compounds having a desired activity to carry out the method of Claim 1, as per Claim 9.

As noted above, Brenner's method involves: (i) carrying out a 'sequential encoding' process for making oligonucleotide-tagged compounds in which synthesis of the compound library involves alternate additions of a nucleic acid sequence "$S_k$" with compound monomers "$A_k$" to generate a library of oligonucleotide-tagged compounds, followed by (ii) screening the tagged compounds to select tagged compounds having a desired activity, followed by (iii) sorting the tagged compounds having a desired activity, followed by (iv) sequencing the tagged compounds using a single base DNA sequencing method to identify the library compound (see, e.g., Brenner Figure 4, and column 11, line 25 – column 12, line 25).

Lerner discloses essentially the same process as Brenner noted above (i-iv) (See, e.g., Figure 2, column 9, line 56 through column 10, line 3). The PCR component of Lerner's method is for amplifying oligonucleotide-tagged compounds of interest for "determining the nucleotide sequence of the identifier oligonucleotide" (See Lerner column 11 lines 39-62, and column 18, lines 13-17). Lerner's disclosure in the Background section (column 2, line 22-32) regarding "serial enrichment" of oligonucleotides by PCR adds nothing. Thus Lerner teaches using PCR to report on the synthetic history of the compound by amplifying and then sequencing the associated nucleic acid material.

Applicant submits that any combination of Brenner in view of Lerner would have resulted in the same 'sequential coding' etc. method taught by both references, with the exception that Lerner teaches using PCR for amplifying oligonucleotide-tagged compounds of interest for sequencing in order identify the attached compound (See Lerner column 18, lines 13-17). Brenner adds nothing.

Both references are completely silent on using the amplification product as the basis to generate a subpopulation of nucleic acid tags for deployment in a further iterative round of synthesis according to Claim 1 (as required by Claim 9).

It is submitted that absent hindsight reconstruction with Applicant's specification as the guide, the cited combination of Brenner in view of Lerner would not have rendered obvious the currently claimed process. Accordingly, Applicant respectfully requests that the rejection of Claims 1, 3-10 and 15-16 under § 103(a) over Brenner in view of Lerner be withdrawn.

***Rosenthal in view of Lerner and Brenner***

Claims 1, 3-10, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenthal et al (WO9321340; 10/28/1993), in view of Lerner et al (US 5,723,598; 3/3/1998; filing date: 6/18/1996 cited in IDS) and Brenner (US 5,635,400; 6/3/1997). The rejection is avoided in part and traversed in part for the following reasons.

The specifics of the rejection are reiterated below from pages 22-23 of the Office Action:

> Rosenthal et al, throughout the publication, teach using immobilized template and template specific primer for DNA sequencing reaction, as discussed above.
>
> Rosenthal et al do not explicitly using PCR to amplify the nucleic acid tags, as recited in **clm 9**. The reference also does not explicitly teach using restriction enzymes to cut the nucleic acid tags, as recited in **clm 10**.
>
> However, Lerner et al, teach using PCR to amplify nucleic acids. The reference teaches amplification of selected DNA using PCR (col. 2, lines 22+). The reference also teaches the advantage of PCR such as allowing "serial enrichment" and subsequent sequencing step of the PCR products (col. 2, lines 22+).
>
> Brenner et al, teach repeating restriction cleaving and ligation (e.g. col. 17, lines 4+), and a restriction site in the oligonucleotide tags (e.g. Figure 4, the "NNNNN" region; col. 11, lines 60+). The Brenner reference also teaches the need to engineer a restriction site in the nucleic acid tag such as the need to release the nucleic acid tag for subsequent reactions (col. 10, lines 6+).
>
> Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to amplify the selected nucleic acid tags using PCR and to engineer a restriction site for repeating restriction and ligation steps.
>
> A person of ordinary skill in the art would have been motivated at the time of the invention to use PCR to amplify the selected nucleic acid tags, because the advantage of the PCR

technology such as allowing serial enrichment of the nucleic acid molecule and subsequent sequencing step, as taught by Lerner et al.

A person of ordinary skill in the art would have been motivated at the time of the invention to engineer a restriction site in the nucleic acid tags for subsequent cleaving and ligation reactions, because the need for releasing the nucleic acid tags for subsequent reactions, as taught by Brenner et al.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications, because the using PCR to amplify nucleic acid molecules, and engineering restriction sites (or cleaving by restriction enzyme) are routine and known in the art as taught by Rosenthal et al, Lerner et al, and Brenner et al.

The Examiner has only articulated a basis for the rejection of Claims 9 and 10. Id. *Rouffett*, 149 F.3d. at 1357-59. Accordingly, Applicant respectfully submits that no *prima facie* case of obviousness has been established, as both Claims 9 and 10 ultimately depend from, and are further limited by the method according to Claim 1, for which no specific basis of rejection is given. In the spirit of expediting prosecution, however, Applicant respectfully submits that Rosenthal taken in view of Lerner and Brenner would not have rendered obvious the claimed methods according to Claims 1, 3-10 and 15-16, much less the specific methods according to either Claim 9 or 10.

For Claim 9, the question of obviousness rests on whether the references when combined as a whole would have rendered obvious a method according to Claim 1 that further includes the limitations of Claim 8 as well as Claim 9 (Claim 9 depends from Claim 8, which depends from Claim1).

For Claim 10, this claim depends from and is limited by the nucleic acid tags of Claim 7, which ultimately depends from and limits the method Claim 1. Thus the question of obviousness turns on whether the combined references as a whole would have rendered obvious a method according to Claim 1 that further includes the additional limitations of Claims 7 and 10.

No combination of Rosenthal in view of Brenner and Lerner teach or suggest (expressly or inherently) a method specifying steps (a) – (f) as in Claim 1 as a whole, much less the method of Claim 1 which is further limited to specific embodiments as in, for example, Claims 9 and 10.

As discussed above, Rosenthal discloses a method for sequencing DNA that involves the following steps: (a) forming a single stranded template comprising the nucleic acid to be sequenced; (b) hybridizing a primer to the template to form a template/primer complex; (c) extending the primer by the addition of a single labeled nucleotide; (d) determining the type of labeled nucleotide added onto the primer; (e) removing or neutralizing the label; and (f) repeating steps (c) to (e) sequentially and recording the order of incorporation of labeled nucleotides.

Rosenthal fails to teach or suggest (expressly or inherently) a method specifying steps (a) – (f) as in Claim 1 as a whole, and thus fails to teach or suggest a method according to Claim 1 which is further limited to specific embodiments as in, for example, Claims 9 and 10.

Brenner discloses single base DNA sequencing for sequencing tagged compounds, which involves various restriction and ligation steps (see, e.g., Brenner Figure 4, and column 11, line 25 – column 12, line 25). Lerner teaches using PCR to amplifying oligonucleotide-tagged compounds of interest for "determining the nucleotide sequence of the identifier oligonucleotide" (See Lerner column 11 lines 39-62, and column 18, lines 13-17). Lerner also discloses in the Background section (column 2, line 22-32) that "serial enrichment" of nucleic acids by PCR for sequencing was known. Thus Brenner and Lerner each teach using sequencing to report on the synthetic history of the compound by either: (1) amplifying and then sequencing the associated nucleic acid material as per Lerner, or by (2) sequencing the associated nucleic acid material using Brenner's single base DNA sequencing method.

For Rosenthal's sequencing method to work, that method, as with Brenner's single base or Lerner's PCR amplified sequencing methods (discussed above and in the responses under §102(b) and §103(a)) requires use of a single template nucleic acid. Lerner's disclosure regarding "serial enrichment" of nucleic acids by PCR adds nothing. Such sequencing methods would be rendered inoperable after even a single round of pooling of different template sequences from one extension reaction and then splitting them based on a completely different template sequence before carrying out a next sequencing reaction would result in non-interpretable output.

Thus the combination of references in the rejection is misguided. Indeed, it is difficult to comprehend the Examiner's rejection and how it is specifically being applied against Applicant's

claims, which manifests itself as a misguided attempt to reconstruct Applicant's invention in hindsight.

In addition, Applicant submits that any combination of Rosenthal, Brenner and Lerner would have resulted in the same 'sequential coding' etc. method taught by Brenner and Lerner, with the exception of how sequencing of a specific tagged-compound is to be carried out (e.g., Rosenthal's sequencing method, the single base DNA sequencing method of Brenner, or using PCR according to Lerner to amplify the material for sequencing).

The references fail to teach or suggest alone or in combination using amplification products from a subpopulation of nucleic acid tags identified from carrying out Applicant's method according to Claim1 and to then use that subpopulation for deployment in a further iterative round of synthesis according to Claim 1 (as required by Claim 9 or Claim 10).

Thus even if Lerner or Brenner may have reasonably suggested to one of ordinary skill in this art to use PCR and/or restriction sites and ligation for sequencing in the method of Rosenthal, the Examiner has failed to provide any evidence and/or reasoning in the record explaining why one of ordinary skill in this art would have modified this teaching of Brenner and Lerner to somehow modify the sequencing method of Rosenthal to arrive at Applicant's claimed method for making a plurality of compounds. Thus, it is manifest that the only direction to Applicant's claimed invention as a whole is supplied by Applicant's own specification. Fine, *supra*; Dow Chem., *supra*.

Accordingly, Applicant respectfully request that the rejection to Claims 1, 3-10 and 15-16 under 35 U.S.C. 103(a) over Rosenthal in view of Lerner and Brenner be withdrawn.

**CONCLUSION**

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-390.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: November 19, 2007

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